KIDNEY& CHOLESTASIS

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Definitions

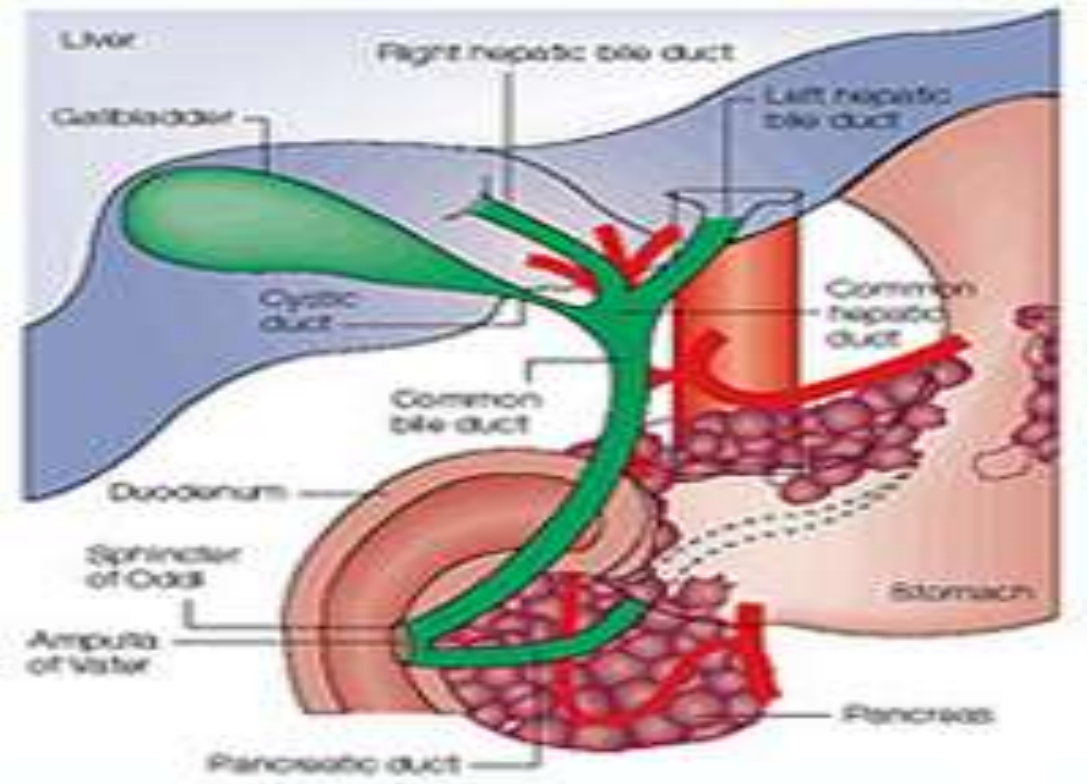
The term cholestasis is Greek in origin, meaning bile stoppage (Heathcote, 2007).

Cholestasis is an impairment of bile formation and/or bile flow which may clinically present with fatigue, pruritus and, in its most overt form, jaundice.

Cholestasis is considered chronic if it lasts >6 months (EASL, 2009). Most chronic cholestatic conditions can progress towards cirrhosis and hepatocellular insufficiency which may require liver transplantation (Poupon et al., 2000).

Causes of cholestasis

Cholestasis is classified as intrahepatic, when the anatomical location of the impairment in bile excretion is somewhere between the hepatocellular cytoplasm and medium-size bile ducts (up to approximately 400 μm in diameter), and extrahepatic when it occurs in the great bile ducts (Pérez et al., 2004).


Liver
Right hepatic bile duct
Left hepatic bile duct
Gallbladder
Cystic duct
Common hepatic duct
Common bile duct
Duodenum
Sphincter of Oddi
Ampulla of Vater
Stomach
Pancreas
Pancreatic duct

Causes of extrahepatic cholestasis (chopra et al., 2011)

Cholangiopathies:

- Cholelithiasis
- Biliary strictures
- Cholangiocellular carcinoma
- Primary sclerosing cholangitis
- AIDS cholangiopathy
- Choledochal cyst
- Sphincter of Oddi dysfunction
- Parasitic infections (Ascaris and Fasciola hepatica)
- Histiocytosis X

Extrinsic causes:

- Pancreatitis (acute and chronic)
- Pancreatic carcinoma
- Portal adenopathy
- Periampullary carcinoma
- Periampullary diverticulum
- Mirizzi's syndrome

Causes of intrahepatic cholestasis in aduls(EASL, 2009)

Hepatocellular cholestasis:

- Sepsis
- Cholestatic viral hepatitis
- Steatohepatitis
- Drug- or parenteral nutrition-induced cholestasis
- Genetic disorders: e.g., Benign recurrent intrahepatic cholestasis , intrahepatic cholestasis of pregnancy.
- Malignant infiltrating disorders
- Benign infiltrating disorders: e.g., amyloidosis, sarcoidosis and storage diseases
- Paraneoplastic syndromes: e.g., Hodgkin disease, renal carcinoma
- Congenital hepatic fibrosis
- Vascular disorders: e.g., Budd–Chiari syndrome, veno-occlusive disease, congestive hepatopathy
- Cirrhosis (any cause)

Cholangiocellular cholestasis:

- Primary biliary cirrhosis
- PSC
- Overlap syndromes of PBC and PSC with autoimmune hepatitis
- IgG4-associated cholangitis
- Idiopathic adulthood ductopenia
- Ductal plate malformations: biliary hamartoma, Caroli syndrome
- Cystic fibrosis
- Drug-induced cholangiopathy
- Graft vs. host disease
- Secondary sclerosing cholangitis, ischemic cholangiopathies, infectious cholangitis related to AIDS

There are many modalities for diagnosis of cholestasis in addition to clinical features including laboratory testes such as; elevated serum bilirubin level with a preponderance of the conjugated fraction is the rule.

The serum gamma glutamyl transpeptidase (GGT) level is also raised in cholestasis. The alkaline phosphatase may be elevated up to ten time's normal (Malhi and Gores, 2006).

Imaging modalities as liver US, CT scan and MRI of the hepatobiliary system should be performed to decide if cholestasis is extrahepatic or intrahepatiic.

If bile ducts appear dilated and the probability of interventional treatment is high, ERCP or trans-hepatic cholangiography (THC) should be the next step.

Once bile duct dilation and space occupying lesions are excluded, a work up for intrahepatic cholestasis should be started (Pérez et al., 2004).

Also, Endoscopic ultrasonography has various applications (Yusuf and Bhutani, 2004).

Cholestasis and kidney

ACUTE RENAL FAILURE

For many years, surgeons were impressed by the frequent complication of hypotension and kidney failure after surgery on patients with obstructive jaundice (Green and Better,1995).

In 1911, Clairmont and von Haberer first described the occurrence of acute renal failure developing after surgery for obstructive jaundice in five patients.

In 1930, Heiwig and Schutz coined the term "hepatorenal syndrome" to describe a set of patients who developed renal failure after biliary tract surgery. (Currently, the term "hepatorenal syndrome is used to define a different clinical condition).

Following these original observations, numerous clinical series have been reported in the literature, all of which point to a strong association between postsurgical renal failure and obstructive jaundice.

Acute renal failure occurs in 8 to 10% of patients requiring surgery for relief of obstructive jaundice and contributes to eventual mortality in 70 to 80% of those who develop it.

The most widely used animal model for obstructive jaundice is **bile duct ligation (BDL) in dog, rat, Rabbit, baboon and cat.**

Within few days hyperbilirubinemia combined with hepatocellular damage occur, After several weeks, however the magnitude of hyperbilirubinemia diminishes and liver disease progresses.

To study the isolated effect of jaundice on kidney function and the circulation in the absence of hepatocellular damage, a surgical anastomosis of the bile duct to the venous systems was done **(choledochocaval anastomosis, CDCA)** in the dog and rat, in them severe jaundice develops within a few days.

Also the effect of isolated cholemia on kidney function and systemic hemodynamics has been studied **by direct infusion of bile constituents (bile, bilirubin or bile acids) into the systemic or renal circulation.**

ALTERED SYSTEMIC HEMODYNAMICS IN OBSTRUCTIVE JAUNDICE

In reviewing retrospectively 100 consecutive cases of obstructive jaundice, Meakin (1932)found that systolic, diastolic, and pulse pressures tended to be lower than those observed in the normal population. Because most of these patients also had bradycardia. it was presumed that the hypo tension is related to the bradycardia.

In 1956, Zollinger and Williams established that jaundiced patients undergoing biliary surgery were more susceptible to a hypotensive crisis and renal failure after hemorrhage during surgery, and this susceptibility could be ameliorated by volume expansion before surgery (Williams et al., 1960).

Both *in vivo* and *in vitro* studies in experimental models have established the vasodilatory properties of jaundice with or without concomitant liver disease.

Cattel and Birnstingl (1967) found that BDL dogs were more prone to hypotension with severe hemorrhage than were same operated animals.

Parenchymal liver damage due to obstructive jaundice may have an independent contrtbutmg role in the pathogenesis of the altered systemic hemodynamics. In patients with chronic liver disease there is refractoriness of the peripheral vascular bed to exogenously administered vasoactive agents (Lunzer et al., 1975).

Morever in spite of systemic hypotension, chronic liver disease is characterized by elevations in plasma and urine concentrations of norepinephrine (ing-Larsen et al., 1982), indicating end-organ unresponsiveness.

This hemodynamic instability has been attributed to the presence of large anatomical arteriovenous shunts. It has also been proposed that several circulating vasodilators that accumulate in this condition could play a role in diminishing the "fullness"of the arteriovenous tree. These vasodilators include bradykinin, substance P., vasoactive intestinal peptide (VIP),glucagon, prostacycline and atrial natrturetic peptide (Bosch et al, 1988). The same results also obtained by Jacob et al. 1993

Experimental studies showed that the effects of obstructive jaundice (bile acids and endotoxins) on the peripheral vasculature in humans and animals are those of decreased vascular resistance with normal or low blood pressure and an exaggerated hypotensive response to volume depletion (Green and Better, 1995)

Impaired Cardiac Performance in Obstructive Jaundice- the ”Jaundiced Heart"

Many *in vitro* and *in vivo* studies have subsequently estabished the negative chronotropic (bradycardia) and inotropic effects of bile acids (Joubert,1978).

It was felt that cholic acid was a functional antagonist of isoprenaline.

Other studies have suggested that the negative chronotropic effect induced by bile acids is mediated through vagal stimulation and can be antagonized by atropine (Ennquez et al.,1985).

In vito and in vivo studies demonstrated a jaundice-induced cardiac myopathy ("the jaundiced heart"). The cellular mechanism may be linked to a depletion of intracellular glycogen and defective energy metabolism within the cardiac myocyte (Taguddin et al., 1980)

In conclusion, the current evidence indicates that obstructive jaundice is associated with impaired cardiac function. Retained bile acids as well as liver damage may contribute, in an independent manner, to negative chronotropic and inotropic effects.

This, in turn, may play a role in the pathogenesis of "underifiling" of the circulation and susceptibility to acute renal failure in patients with obstructive jaundice.

EFFECT OF OBSTRUCTIVE JAUNDICE ON KIDNEY FUNCTION

When the natural excretory route of bile is blocked, the kidney becomes the main excretory organ for the retained bile substances.

Various studies showed conflicting changes in GFR or RBF in patients and animals with obstructive jaundice and this may results from the use of anesthetics that are known to affect both RBF and GFR (Mazze et al., 1963).

Also, in different animal models, altered cardiovascular function in obstructive Jaundice could have an independent adverse effect on kidney function.

In dogs, both the direct venous infusion of bile and infusion in the renal artery have been shown to result in increased urinary flow and sodium excretion without changing GFR or RBF (Finestone et al, 1984).

Moreover, acute (4-h) BDL in dogs (acute cholemia without liver disease) actually increases GFR and RBF (Levy and finestone 1983).

Also, In dogs with CDCA (a "pure" cholemia model), GFR and RBF are preserved in the face of systemic hypotension (Alon et al., 1984), indicating again *the lack of a direct deleterious effect of bile on the kidney.*

The previous studies demontrated that, ***the high prevalence of postsurgery acute renal fallure and mortality in patients with extra-hepatic cholestasis has its origin extrarenally.***

Thus events occuring during surgery (hemorrhage, hypotension and anesthesia) may play in concert with jaundice and "arterial underfilllng" (due to reduced peripheral vascular resistance and impaired cardiac function) to compromise kidney function in the postoperative period.

DIURETIC AND NATRIURETIC EFFECT OF BILE SALTS: A POTENTIAL CAUSE FOR HYPOVOLEMIA IN OBSTRUCTIVE JAUNDICE

Studies of Finestone et al,(1984) have shown that the intrarenal infusion of bile in dogs is associated with an increase in fractional Na excretion, urine flow, and K excretion. Likewise, BDL in rats for 6 days resulted in increased Na excretion (Heidenreich et al., 1987)

So studies showed that, **cholemla, per se, has diuretic and natriuretic properties, which serve as a potential cause for hypovolemia and prerenal disease** in patients with obstructive jaundice.

ENDOTOXEMIA, LIVER DISEASE, AND OBSTRUCTIVEJAUNDICE

The evidence remains **equivocal** for involving endotoxin in the pathogenesis of renal dysfunction associated with obstructive jaundice in human patients.

Gatta and colleagues (1982), in a careful study of systemic endotoxemia and renal function in cirrhosis, found no difference in the frequency of endotoxemia in patients with and without impaired RBF

Summary

The current evidence, mainly derived from experimental models and to less extent from patient studies, indicates that jaundice alone (i.e.,independent of liver parenchymal disease) affects the integrity of the cardiovascular function. These effects are :

(1) reduction in peripheral vascular resistance which results in systemic hypotension.

(2)depression of myocardial performance; and

(3) an initial and profound natriuresis and diuresis that may lead to volume depletion.

Furthermore most of the experimental data suggest that neither bilirubin nor bile acids have a direct nephrotoxic effect, and therefore renal complications in experimental obstructive jaundice are mainly due to **prerenal factors.**

Gubern et al study (1988) reported that mannitol did not improve the postoperative renal function in patients who were already impaired before surgery and it worsened that who had normal creatinine clearances before surgery as further water depletion may be induced.

Hence, the maintenance of circulating extracellular volume is the mainstay of treatment and prophylaxis in jaundiced patients undergoing surgery.

It is also noted that, that operative mortality declined if preoperative blood transfusions were given to keep hematocrite normal.

In addition, careful preoperative evaluation and both intraoperative and postoperative monitoring of fluid status and cardiac performance should be performed.

NSAID should be avoided as these drugs can cause a marked decrease in both RBF and creatinine clearance (Green and Better, 1995)

Endoscopic biliary decompression (ERCP) is a useful alternative to surgery for risky patients with extra-hepaic cholestasis.

BILE CAST NEPHROPATHY

Cholemic nephrosis represents a spectrum of renal injury from proximal tubulopathy to intrarenal bile cast formation found in patients with severe liver dysfunction.

It is unclear why cholemic nephrosis has been largely forgotten in the modern medical literature(Charle et al., 2013).

In the past decade, there are only three reports of four patients with cholemic nephrosis(Song and Chang, 2009 and Bredewold et al., 2011)

However, tubular bile cast formation is not a new concept, as most studies of cholemic nephrosis occurred between 1920 and 1970.

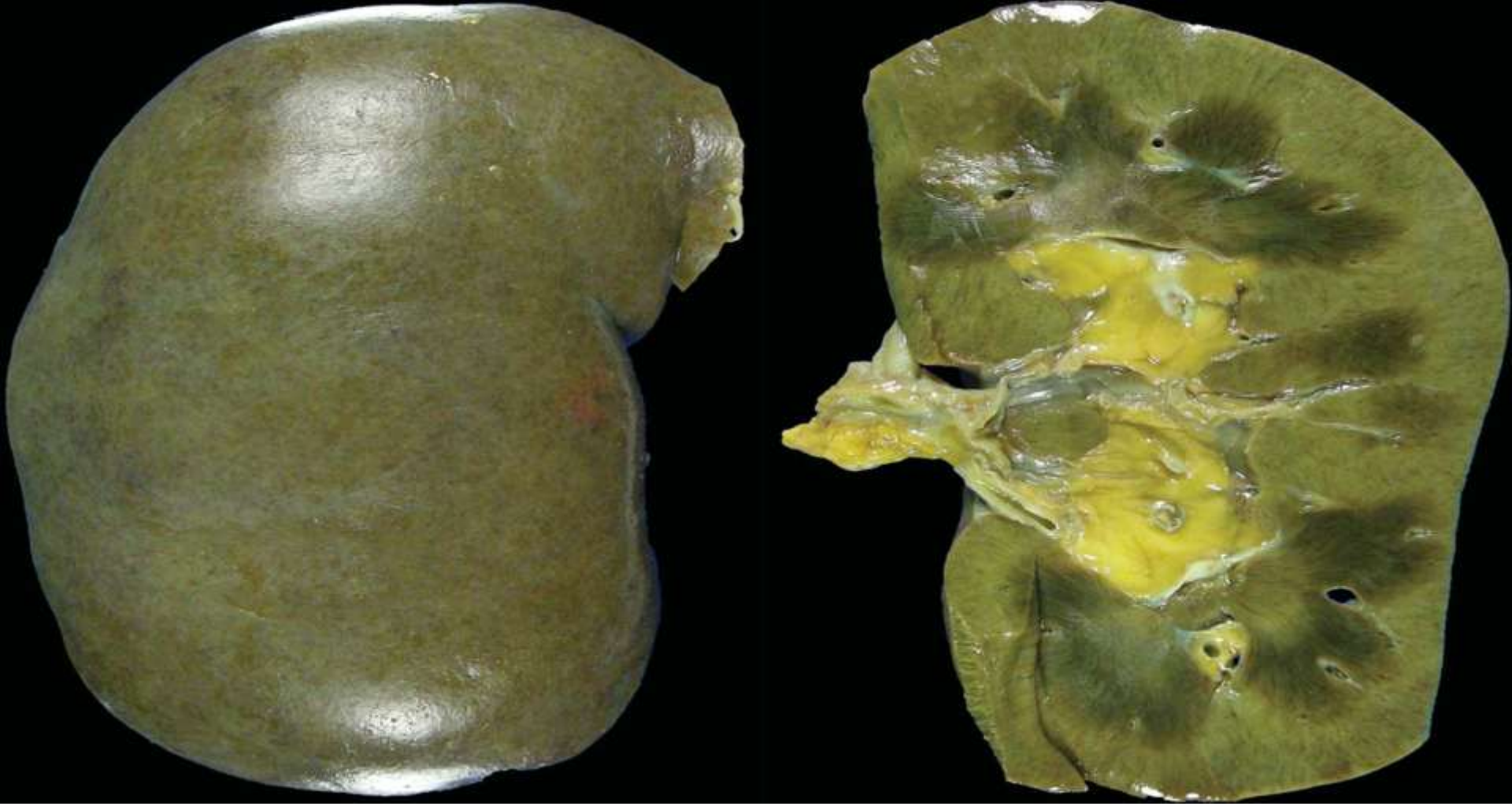
De Tezanos et al.(1969) found renal bile casts in 13 (12%) of 105 patients with liver disease and renal dysfunction, which is similar to the % of cases in van Slambrouck et al study (2013) with severe bile cast formation.

Also studies of Bal et al(2000), Shet et al(2002) and Lee et al (2009) identified bile casts in cases with subacute hepatic failure (autopsy), biliary cirrhosis and acute ischemic liver injury respectively.

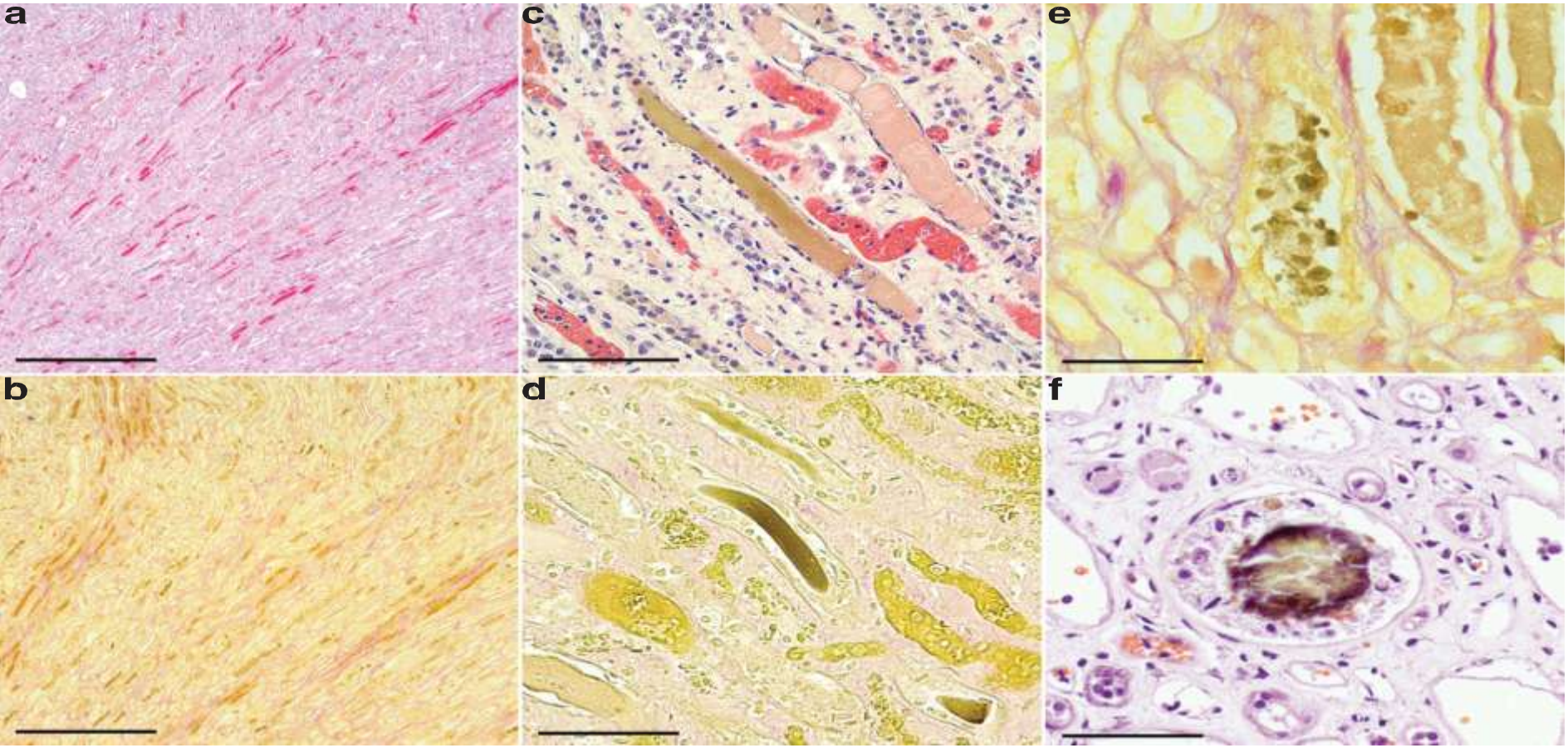
Betjes and Bajema (2006) suggested jaundice-related nephropathy as a replacement for cholemic nephrosis, which similar to the replacement of lipoid nephrosis by minimal change disease.

Based on their definition, jaundice-related nephropathy would encompass the spectrum of injury that ranges from proximal tubulopathy to extensive tubular injury and tubular pigment.

van Slambrouck et al (2013) propose that bile cast nephropathy is an appropriate pathologic term, which emphasizes the severe end of the spectrum of the renal injury in this unique clinical setting.



THE GREEN DISCOLORATION OF THIS KIDNEY AT AUTOPSY IS BECAUSE OF THE CONVERSION OF BILIRUBIN TO BILIVERDIN AFTER FORMALIN FIXATION. THE RENAL PYRAMIDS SHOW A DARKER GREEN COLOR AS THE CONCENTRATION OF BILIRUBIN IS HIGER COMPARED WITH THE CORTEX. LINEAR GREEN STREAKS CONSISTENT WITH BILE CASTS CAN ALSO BE SEEN THROUGHOUT THE CORTEX AND MEDULLA.



Histopathologic findings in bile cast nephropathy. (a)Numerous pink tubular casts(b)A Hall stain highlights many green–yellow tubular casts (c)Yellowish green acellular tubular cast in the distal nephron of the medulla is characteristic of a bile cast (d)Bilirubin in several tubular casts(e)Pigmented sloughed tubular epithelial cells (Hall stain (f) Bile-stained calcium oxalate crystal are occasionally present(H&E).

In summary, bile cast nephropathy is an important pathologic entity that may account for the renal function impairment of many patients with severe liver dysfunction.

It can occur in a wide spectrum of liver disorders and in both pediatric and adult population as well as in patients with or without cirrhosis.

Of interest, all 10 patients in van Slambrouck et al study (2013) with cirrhosis due to alcohol abuse had bile casts, whereas none of the 5 patients with post-HCV cirrhosis had bile casts, but further studies need to be performed to validate this observation.

Kidney biopsy is necessary to diagnose bile cast nephropathy.

Additional studies are needed to establish the significance of this parameter for patient management in different clinical settings.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